



**REMARKS**

Entry of the foregoing, reexamination, and reconsideration of the subject application, pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested in light of the following.

**Status**

As is correctly reflected in the Office Action Summary, Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-11 are pending. *Office Action mailed May 28, 2010, Office Action Summary, Item 4 (including Continuation Sheet).* Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-11 were rejected. *Id. at Item 6 (including Continuation Sheet).*

**Summary of Claim Amendments**

By the foregoing claim amendments, Applicants amended Claims 77 and 87 to correct a minor/typographical error. Specifically, Claims 77 and 87 were amended to conclude with “comprise acceptors.” Support for these amendments may be found throughout the Specification. Accordingly, no new matter has been added.

**Specification – Bibliographic Information**

The Examiner objected to the Specification for failing to provide sufficient bibliographic information for the cited publications. See *Office Action mailed May 28, 2010, Pages 2-3, ¶¶ 3-4*. These objections are respectfully traversed.

Not to acquiesce in the Examiner's objections, but solely to facilitate prosecution, by the foregoing amendments Applicants replaced the Specification on file with the appended Substitute Specification (appended in both clean and marked-up formats). The appended Substitute Specification includes detailed bibliographic information for the cited publications. The detailed bibliographic information was readily-determinable based on the information provided with the original Specification. Accordingly, one of ordinary skill in the art could readily determine the now-explicit detailed bibliographic information and, as such, no new matter has been added.

In view of the foregoing, Applicants respectfully request withdrawal of the objections to the Specification based upon insufficient bibliographic information.

**Specification – Description of the Drawings**

The Examiner objected to Page 31 of the Specification, at "DESCRIPTION OF THE DRAWINGS," for purportedly failing to include a description of Figures 7-12. See *Office Action mailed May 28, 2010, Page 3, ¶ 5a*. This objection is respectfully traversed.

In an Amendment and Response filed on April 3, 2003, the Specification was amended to include a description of Figures 7-12. See *Response to 21 January 2003*

*Non-Final Office Action, Pages 3, 4, 23, 24.* Accordingly, Applicants believe the objection issued in error.

However, solely to facilitate prosecution, by the foregoing amendments Applicants replaced the Specification on file with the appended Substitute Specification (appended in both clean and marked-up formats). The appended Substitute Specification includes a description of all Figures.

In view of the foregoing, Applicants respectfully request withdrawal of the objection to the Specification based upon the alleged lack of description of Figures 7-12.

**Specification – Graphic Inserts On Pages 55 and 56**

The Examiner objected to Pages 55 and 56 of the Specification due to the inclusion of “graphic inserts/cells of chemical formulae and reactions” thereon. See *Office Action mailed May 28, 2010, Pages 3-4, ¶ 5b.* These objections are respectfully traversed.

Not to acquiesce in the Examiner’s objections, but solely to facilitate prosecution, by the foregoing amendments Applicants replaced the Specification on file with the appended Substitute Specification (appended in both clean and marked-up formats). The appended Substitute Specification does not include the graphic inserts/cells from original Pages 55 and 56. Instead, these three (3) inserts/cells have been removed and are now Figures 13, 14, and 15, respectively.

In view of the foregoing, Applicants respectfully request withdrawal of the objections to the Specification based upon the graphic inserts/cells on original Pages 55 and 56 of the original Specification.

### **Substitute Specification**

Pursuant to 37 C.F.R. § 1.125, by the foregoing amendments Applicants replaced the Specification on file with the appended Substitute Specification (appended in both clean and marked-up formats). The clean copy of the Substitute Specification reflects all amendments made to date. *See Manual of Patent Examining Procedure (“M.P.E.P.”) § 608.01(q).* The marked-up copy of the Substitute Specification shows all changes made to date relative to the immediately-prior version of the Specification of record, *i.e.*, the original Specification. *Id.* Applicants submit that the Substitute Specification does not include new matter.

### **Drawings**

The Examiner requested that corrected drawings be furnished for the instant application. *See Office Action mailed May 28, 2010, Pages 4-5, ¶¶ 7-8.*

Not to acquiesce in the Examiner’s request, but solely to facilitate prosecution, by the foregoing amendments Applicants replaced existing Figures 1-12 with Replacement Figures 1-12 and added new Figures 13-15. Figures 1-15 comply fully with 37 C.F.R. § 1.84 in that the lettering used is of proper size, is of uniform density, and is well-defined. In addition, the lines in Figures 1-15 are clean, well-defined, and of uniform

thickness. The images/photographs in Figures 1-15 are of high quality and are reproducible in a printed patent. Applicants thank Examiner Sisson for reviewing Figures 1-15 prior to this submission and for verifying the acceptability of Figures 1-15.

Applicants submit that Replacement Figures 1-12 and new Figures 13-15 satisfy the requirements of 37 C.F.R. § 1.84 and do not include new matter.

### **Claim Rejections Under 35 U.S.C. § 103**

Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-11 were rejected under 35 U.S.C. § 103(a) as purportedly obvious over U.S. Patent No. 6,982,146 to Schneider *et al.* ("Schneider") in view of U.S. Patent No. 7,037,687 to Williams *et al.* ("Williams *et al.*") and U.S. Patent No. 6,306,607 to Williams ("Williams"). See *Office Action mailed May 28, 2010, Pages 5-11, ¶¶ 9-32*. These rejections are respectfully traversed at least because Schneider and Williams cannot be combined as the Examiner suggests because their teachings are incompatible and the proposed combination would result in an inoperable method. Under established precedent, such a combination cannot support an obviousness rejection.

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a).

Underlying factual determinations in an obviousness analysis include (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of nonobviousness. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1369 (Fed. Cir. 2005) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

Applicants respectfully submit that a *prima facie* case of obviousness against Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111 due to Schneider in view of Williams *et al.* or Williams has not been made.

It is important to recognize that each of Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111 must be considered *as a whole*. See, e.g., *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 ( 2007) ("What matters is the objective reach of the claim."); *Datascope Corp. v. SMEC, Inc.*, 776 F.2d 320, 324 (Fed. Cir. 1985) (noting that the references must be considered "as a whole" and that the claimed subject matter must be considered "as a whole."). Considering each of Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111 as a whole is important because "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S. Ct. at 1741. That is because "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*

Applicants respectfully submit that only by using impermissible hindsight would one modify Schneider, Williams *et al.*, and Williams as the Examiner suggests to arrive at Applicants' Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111. Yet, factfinders must avoid the distortion caused by hindsight bias "and must be cautious of arguments reliant upon *ex post* reasoning." *KSR*, 127 S. Ct. at 1742 (citing *Graham* and "warning against a 'temptation to read into the prior art the teachings of the invention in issue' and instructing courts to 'guard against slipping into the use of hindsight.'").

The principle of operation of Schneider is a FRET interaction between a donor on a polymerase and an acceptor on a nucleotide. However, the Examiner admits that Schneider does not teach that the fluorescent label is released from the nucleotide by action of the polymerase (see *Office Action mailed May 28, 2010, Page 8*, ¶ 23) and that neither Schneider nor Williams *et al.* have been found to disclose using a nucleotide where the fluorescent label is attached to a terminal phosphate. See *Office Action mailed May 28, 2010, Page 9*, ¶ 28.

Williams is alleged to teach a nucleotide comprising a label attached to a terminal phosphate. However, that is not a complete description of the teachings of Williams. Williams only teaches nucleotides comprising a fluorophore attached to the  $\gamma$ -phosphate that also comprise a quencher moiety. See *Williams at Abstract; at Column 3, Lines 36-58*. The principle of operation of Williams is detection of the fluorescent label after it is released from the quencher.

Thus, the principle of operation of the method of Schneider is incompatible with the principal of operation of the method by Williams. ***Combination of each with the other would defeat the principle of both.*** The presence of the quencher moiety of Williams nucleotides would defeat the principle of FRET transfer between the donor and acceptor in the method described by Schneider. Modification of the Williams nucleotides to remove the quencher moiety would render the nucleotides unsuitable for their intended purpose. Because of this, one of ordinary skill in the art, prior to Applicants' invention, would not have modified Schneider and Williams as the Examiner suggests.

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. The Federal Circuit's comments in *McGinley v. Franklin Sports, Inc.*, are instructive:

We have noted elsewhere, as a "useful general rule," that references that teach away cannot serve to create a prima facie case of obviousness. *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130 (Fed. Cir. 1994). ***If references taken in combination would produce a "seemingly inoperative device," we have held that such references teach away from the combination and thus cannot serve as predicates for a prima facie case of obviousness.*** *In re Sponnoble*, 405 F.2d 578, 587, 160 USPQ 237, 1244, 56 C.C.P.A. 823 (1969) (references teach away from combination if combination produces seemingly inoperative device); see also *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984) (inoperable modification teaches away).

*McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1353-54 (Fed. Cir. 2001) (emphases added); see also *Tec Air, Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360 (Fed.

Cir. 1999) (noting that there "is no suggestion to combine, however, if a reference teaches away from its combination with another source" and that "[i]f when combined, the references 'would produce a seemingly inoperative device,' then they teach away from their combination."). Removal of the quencher moiety from the Williams nucleotides would be contrary to the principle of operation taught in Williams and would render the nucleotides unsatisfactory for their intended purpose.

Thus, either way one considers the proposed combination of Schneider and Williams, there could not have been any motivation to modify the publications as would be required to make the proposed combination. Williams *et al.* has not been alleged and does not cure the deficiencies of Schneider and Williams.

Because a *prima facie* case of obviousness against Claims 10, 16-18, 50, 51, 53-55, 64, 65, 67-69, 71, 72, 74, 76, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106, and 108-111 based upon Schneider, Williams *et al.*, and Williams has not been made, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection thereof.

**CONCLUSION**

In the event that there are any questions relating to this Amendment And Reply After Final Rejection Pursuant To 37 C.F.R. § 1.116, or to the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 836-6620 so that prosecution of the application may be expedited.

The Patent Office is hereby authorized to charge any necessary fees, or credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,  
BUCHANAN INGERSOLL & ROONEY PC

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